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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/560,803	04/28/00	YOUNG W	P04014US1

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EXAMINER	
WINKLER,U	
ART UNIT	PAPER NUMBER
1648	7

DATE MAILED: 10/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/560,803	YOUNG ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *11-13,15-25,34 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14,26-33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that it would not be a burden to search all non-elected groups and that all non-elected groups a simply components to be used in this method. This is not found persuasive because each component requires a different search of the art as shown by their divergent subject matter and different classifications.

The requirement is still deemed proper and is therefore made FINAL.

Specification

2. Applicant is required to update the status (pending, allowed, ect.) of all parent priority applications in the first line of the specification.

3. The attempt to incorporate subject matter into this application by reference to an embedded hyperlink and/or browser-executable code is improper and the links must be deleted, see page 21 lines 27-28 of the instant application. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. As a cautionary note, this may not be the only occurrence of an embedded hyperlink in the specification, applicant is required to check the entire specification for the appearance of hyperlinks in the text and to make the appropriate correction.

Drawings

4. The drawings are objected to because the contain minor informalities, please see notice of Draftsperson's Review. Correction is required.

5. This application has been filed with an informal drawing, figure 10, which is acceptable for examination purposes only. A formal drawing will be required when the application is allowed.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or are listed on applicant's PTO-1449 form they have not been considered.

7. An initialed and dated copy of applicant's IDS form 1449, Paper No. 4, is attached to the instant office action.

Claim Objections

8. Claim 35 is objected to because of the following informalities: It appears that 'internalization' is misspelled as "internation". Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-10, 14, 26-33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "increasing" is indefinite because the ordinary artisan would not know how to determine the requisite quantity necessary to be considered "increasing" and what this value is compared to.

11. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "helper virus " in claims 1-10, 14, 26-33 and 35 is used by the claim to mean "any packaging deficient vector or nucleotide sequence encoding a viral structural protein," while the accepted meaning is "those viruses such as Ad, HSV, cytomegalovirus and pseudorabies virus that serve as complete helpers to AAV."

12. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "viral vector " in claims 1-10, 14, 26-33 and 35 is used by the claim to mean "any viral based vector that does not contain all structural proteins and is replication incompetent" while the accepted meaning of "a viral vector is that it contains all the elements necessary to infect and replicate in a host cell."

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. Claims 1, 6-10, 14, 26 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Gram et al. (Journal of Hematotherapy, 1998).

The instant invention is drawn to a method of increasing viral titer in a packaging cell by contacting the packing cell with a "viral vector" and inhibiting methylation of the LTR promoter to increase the amount of "helper virus" in a cell.

Gram et al. disclose a MLV-derived retroviral vector that encodes two genes hGFP and Neo. Expressing hGFP in a host cell is desirable because it allows for the use of the "viral vector" in viral pathogenesis studies. The replication deficient MLV-derived retroviral vector is inserted into the PG13 packaging cell line (for a complete description of this cell line refer to U.S. Pat. No. 5,766,945). This packaging cell line provides the requisite structural proteins, under the control a retroviral LTR, allowing for the production of replication incompetent recombinant viral particles. DNA demethylation of the transformed packaging cell line with 5-azacytidine, results in an increase in the transcriptions and expression of the "viral vector", indicating that DNA methylation leads to the silencing of gene expression. Treatment with 5-azacytidine of the transformed packaging cells results in the increase of hGFP expression of 36% (see page 337). The ability of the retroviral promoter LTR sequences to become methylated is an inherent property of the promoter and is known to result in reduced expression from that promoter. Supplying a cell with a demethylating agent will result in demethylation of all LTR promoters

present in the cell and thereby resulting an increased expression from all LTR promoter in the cell.

Therefore, the instant invention is anticipated by Gram et al.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claim 1-10, 14 26-33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (U.S. Pat. No. 5,766,945) and Gurtu et al. (BBRC 1996) in view of Gram et al. (J. of Hematotherapy 1998)

The instant invention is drawn to a method of increasing viral titer in a packaging cell by contacting the packing cell with a "viral vector" and inhibiting methylation of the LTR promoter to increase the amount of "helper virus" in a cell.

Miller et al. teach the production of retroviral packaging cell lines in which the structural genes, specifically *env* are driven from the LTR promoter (see figure 1 and the specification). In addition, the reference teaches the production of replication incompetent viral particles and the incorporation of heterologous sequences. The reference does not teach providing a selection marker located on the same mRNA molecule through the use of an internal ribosomal entry site.

Gurtu et al. teach the expression of two genes from the same mRNA molecule by utilizing an internal ribosome entry site from a picornavirus (see figure 1 and 2). The reference generally teaches that this procedure would improve the production of stable mammalian cell lines because those cell that do not express the gene of interest would be eliminated by the selection pressure of the antibiotic. Conventional transfection methods require the transfections of a host cell line with two expression cassettes, one expressing the protein of interest and the other expressing a selectable marker. The disadvantage of the standard method is that the gene expression is generally low because the selective pressure is only on the cassette that expresses

the antibiotic resistance marker. Expression levels of the protein of interest tend to decrease over time. The reference teaches that utilizing the internal ribosome entry site allows for the selective pressure provided by the antibiotic to be exerted on the entire expression cassette, therefore high dose of antibiotic will select only for those cells expressing high level the protein of interest.

Gram et al. teach a MLV-derived retroviral vector that encodes two genes hGFP and Neo. Expressing hGFP in a host cell is desirable because it allows for the use of the "viral vector" in viral pathogenesis studies. The replication deficient MLV-derived retroviral vector is inserted into the PG13 packaging cell line (for a complete description of this cell line refer to U.S. Pat. No. 5,766,945). This packaging cell line provides the requisite structural proteins, under the control a retroviral LTR, allowing for the production of replication incompetent recombinant viral particles. DNA demethylation of the transformed packaging cell line with 5-azacytidine, results in an increase in the transcriptions and expression of the "viral vector", indicating that DNA methylation leads to the silencing of gene expression. Treatment with 5-azacytidine of the transformed packaging cells results in the increase of hGFP expression of 36% (see page 337). The ability of the retroviral promoter LTR sequences to become methylated is an inherent property of the promoter and effects all LTR promoters in the cell. Treating a cell with 5-azacytidine will result in demethylation of all LTR promoters resulting in an increased transcription from the promoter. The reference does not teach using an internal ribosomal entry site in expressing the gene of interest or expressing the viral structural protein from the packaging cell line.

It would have been obvious to one of ordinary skill in the art to produce a retroviral packaging cell line utilizing retroviral LTR as the promoter according to the methods described

by Miller and including the efficiency of the selectable markers utilizing an internal ribosome entry site from a picornavirus as taught by Gurtu et al. Providing a compound that demethylates DNA as taught by Gram et al. would allow for the most efficient transcription from the LTR promoter resulting in increased viral production in the system taught Miller, Gurtu et al. and Gram et al. One having ordinary skill in the art would have been motivated to do this in order to maximize the production of recombinant viral particles obtained from the packaging system. Therefore, the instant invention is obvious over Miller and Gurtu et al. in view of Gram et al.

Conclusion

19. Claims 1-10, 14, 26-33 and 35 are rejected.

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Beach et al. U.S. Pat. No. 6,025,192.

Challita et al. Multiple modifications in cis elements of the LTR of retroviral vectors lead to increased expression and decreased DNA methylation in embryonic carinoma cells. Journal of Virology (1995) Vol. 69, No. 2, pp. 748-755.

Miller et al. Retrovirus packaging cell pbased on 10A1 Murine leukemia virus for production of vectors that use multiple recptors for cell entry. Journal of Virology (1996) Vol. 70, No. 8, pp. 5564-5571.

Levenson et al. Internal ribosomal entry site-containing retroviral vectors with green fluorescent protein and drug resistance markers. Human Gene Therapy (1998) Vol. 9, pp. 1233-1236.

Sugimoto et al. In vivo drug-selectable markers in gene therapy. Leukemia (1997) Supp. 3, pp. 552-556.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 or for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

Jeffrey Stucker

JEFFREY STUCKER
PRIMARY EXAMINER